PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4239-68223-01	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/US2004/010588	International filing date *(day/month/year)* 05.04.2004	Priority date *(day/month/year)* 08.04.2003
International Patent Classification (IPC) or national classification and IPC C07K14/47, G01N33/574		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AM... et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.11.2004	26.07.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Grötzinger, T Telephone No. +49 89 2399-7166

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/010588

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-59	as originally filed
Sequence listings part of the description, Pages	
1-9	as originally filed
Claims, Numbers	
1-46	as amended (together with any statement) under Art. 19 PCT
Drawings, Sheets	
1/6-6/6	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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PCT/US2004/010588

Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
   - ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).
   - ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 26-38,42-44

   because:

   ☒ the said international application, or the said claims Nos. 26-38,42-44 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

   ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

   ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

   ☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-46
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-46
Industrial applicability (IA)	Yes:	Claims	1-46
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item II.

The priority document that has been filed in connection with the present application is US application 60/461,339, filed on 8 April 2003 in the name of B. Case and R. Paul. However, the application whose priority has been claimed by the present application is US application 60/461,399, filed on 8 April 2003.
Consequently, it has not been possible to consider the validity of the priority claim. This report has nevertheless been established on the assumption that the relevant date is the claimed priority date.

Re Item III.

For the assessment of the present claims 26 to 38, and 42 to 44 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment or diagnostic methods, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V.

The following documents are referred to in this communication:

D1 = WO99/67384
D2 = Database accession no. BC047903

1. Inventive Step (Article 33(3) PCT)

1.1 Claims 1 to 46
Claims 1 to 46 are not inventive as required by Article 33(3) PCT.
Prostate cancer-associated genes and polypeptides were well known in the prior art from, e.g., WO99/67384 (D1) (see, e.g., the abstract).
Starting from this closest prior art, the technical problem underlying the present

application could be seen in the provision of further prostate-specific proteins.
This problem is solved by providing the nucleic acid molecules/proteins of SEQ ID NOs: 2 and 1.
However, this solution is obvious in view of the disclosure content of BC047903 (D2). This document discloses a partial cDNA sequence encoding a human "prostate cancer associated protein 5" that is 100% identical to the 3'-terminal 461 nucleotides of the sequence of SEQ ID NO:2 of the present application. For solving the above technical problem, BC047903 (D2) thus provided an ideal starting point for the person skilled in the art: It provided the motivation since the cDNA was only partial, and certainly, there was also a reasonable expectation of success to isolate the full-length cDNA sequence. It thus appears as if the person skilled in the art would have arrived at the claimed products without further ado.

Claims 2 to 46 represent standard molecular biology applications. Insofar as they are new over the cited prior art, they thus do not involve an inventive step.

Therefore, claims 1 to 46 do not comply with the requirements of Article 33(3) PCT.

Re Item VIII.

2. Clarity (Article 6 PCT)

2.1 In various claims the term "homologous" is used. However, "homology" with respect to amino acid sequences is ambiguous because it is unclear whether identity or similarity is meant, and with respect to nucleic acid sequences it is meaningless because only the degree of identity can be established between two nucleic acid sequences.

2.2 The indication of the percentage of identity is only meaningful if the regions that are compared are defined.

2.3 In claims 1 and 32 the phrase "wherein the isolated polypeptide is eight to ten..." is ambiguous because it refers to "the isolated polypeptide" although the at least eight consecutive amino acids are apparently meant.

2.4 SEQ ID NOs:1 and 2 show single specific sequences. Thus, the indefinite articles "an/a" in claims 1(3), 5, 7, 22, and 32(3) are not appropriate.

CLAIMS

1. An isolated polypeptide comprising:

(1) an amino acid sequence at least 90% homologous to SEQ ID NO: 1;

(2) at least eight consecutive amino acids of amino acids 157-933 of SEQ ID NO: 1, wherein the isolated polypeptide is eight to ten amino acids in length and binds an MHC molecule; or

(3) an amino acid sequence set forth as SEQ ID NO: 1.

2. The isolated polypeptide of claim 1, comprising a polypeptide having an amino acid sequence at least 90% homologous to SEQ ID NO: 1.

3. The isolated polypeptide of claim 2, comprising an amino acid sequence at least 95% homologous to SEQ ID NO: 1.

4. The isolated polypeptide of claim 1, comprising at least eight consecutive amino acids of amino acids 157-933 of SEQ ID NO: 1, wherein the isolated polypeptide is eight to ten amino acids in length and binds an MHC molecule.

5. The isolated polypeptide of claim 1, comprising an amino acid sequence as set forth as SEQ ID NO: 1.

6. An isolated nucleic acid sequence encoding the polypeptide of claim 1.

7. The isolated nucleic acid sequence of claim 6, comprising a sequence as set forth as SEQ ID NO: 2, or a degenerate variant thereof.

8. The isolated nucleic acid sequence of claim 6, operably linked to a promoter.

9. An expression vector comprising the nucleic acid sequence of claim 6.

10. A host cell transfected with the nucleic acid sequence of claim 6.

11. The host cell of claim 10, wherein the host cell is a mammalian cell.

12. An antibody that specifically binds the polypeptide of claim 1.

13. The antibody of claim 12, wherein the antibody is a monoclonal antibody.

14. The antibody of claim 12 comprising a detectable label.

15. The antibody of claim 12, wherein the label is a fluorescent, enzymatic or radioactive label.

16. The antibody of claim 12 conjugated to a toxin.

17. A method for detecting prostate cancer in a subject, comprising

contacting a sample obtained from the subject with the antibody of claim 12 for a sufficient amount of time to form an immune complex;

detecting the presence the immune complex, wherein the presence of an immune complex demonstrates the presence of prostate cancer in the subject.

18. The method of claim 17, wherein the sample is a biopsy, blood, serum, or urine sample.

19. The method of claim 17, wherein the sample is a biopsy sample of non-prostate origin.

20. The method of claim 17, wherein the antibody is labeled.

21. A method for detecting a prostate cancer in a subject, comprising

detecting the expression of the polypeptide of claim 1 in a sample from the subject, wherein an increase in the expression of the polypeptide as compared to a control indicates the presence of the prostate cancer.

22. The method of claim 21, wherein detecting the expression of polypeptide comprises detecting a polypeptide having a sequence set forth as SEQ ID NO: 2 in the sample.

23. The method of claim 22, wherein detecting the expression of the polypeptide comprises

contacting the sample with an antibody that specifically binds the polypeptide for a sufficient amount of time to form an immune complex; and

detecting the presence of the immune complex.

24. The method of claim 21, wherein detecting the expression of the polypeptide comprises detecting the presence of mRNA encoding the polypeptide.

25. The method of claim 24, wherein detecting the presence of mRNA encoding the polypeptide comprises a Northern Blot analysis, an RNA Dot blot, or a reverse transcriptase polypermase chain reaction (RT-PCR) assay.

26. A method for producing an immune response against a cell expressing a polypeptide of claim 1 in a subject, the method comprising

administering to the subject a therapeutically effective amount of the polypeptide of claim 1, or a polynucleotide encoding the polypeptide, thereby producing the immune response.

27. The method of claim 26, wherein the immune response is a T cell response.

28. The method of claim 26, wherein the immune response is a B cell response.

29. The method of claim 26, wherein the subject has prostate cancer.

30. The method of claim 29, wherein the immune response decreases the growth of the prostate cancer.

31. A method for inhibiting the growth of a malignant cell expressing the polypeptide of claim 1, the method comprising,

(i) culturing cytotoxic T lymphocytes (CTLs) or CTL precursor cells with the polypeptide of claim 1 to produce activated CTLs or CTL precursors that recognize an NGEP expressing cell, and

(ii) contacting the malignant cell with the activated CTLs or CTLs matured from the CTL precursors,

thereby inhibiting the growth of the malignant cell.

32. A method for inhibiting the growth of a malignant cell, comprising:

contacting the malignant cell with an effective amount of a cell-growth inhibiting molecule, wherein the cell growth inhibiting molecule comprises an antibody which specifically binds a polypeptide comprising

(1) an amino acid sequence at least 90% homologous to SEQ ID NO: 1;

(2) at least eight consecutive amino acids of amino acids 157-933 of SEQ ID NO: 1, wherein the isolated polypeptide is eight to ten amino acids in length and binds an MHC molecule; or

(3) an amino acid sequence set forth as SEQ ID NO: 1;

wherein the antibody is covalently linked to an effector molecule which inhibits the growth of cells,

thereby inhibiting the growth of the malignant cell.

33. The method of claim 32, wherein said antibody is a monoclonal antibody.

34. The method of claim 32, wherein the effector molecule is a chemotherapeutic agent.

35. The method of claim 32, wherein the effector molecule comprises a toxic moiety.

36. The method of claim 35, wherein the toxic moiety is selected from the group consisting of ricin A, abrin, diphtheria toxin or a subunit thereof, *Pseudomonas* exotoxin or a portion thereof, saporin, restrictocin or gelonin.

37. The method of claim 35, wherein the *Pseudomonas* exotoxin is selected from the group consisting of PE35, PE37, PE38, and PE40.

38. The method of claim 35, wherein the malignant cell is *in vivo*.

39. A pharmaceutical composition comprising a therapeutically effective amount of the polypeptide of claim 1 in a pharmaceutically acceptable carrier.

40. A pharmaceutical composition comprising a therapeutically effective amount of the polynucleotide of claim 6 in a pharmaceutically acceptable carrier.

41. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of claim 12 in a pharmaceutically acceptable carrier.

42. A method for reducing the number of prostate cancer cells in a subject, comprising

administering to the subject a therapeutically effective amount of the polypeptide of claim 1, wherein the administration of the NGEP results in an immune response to NGEP,

thereby reducing the number of prostate cancer cells in the subject.

43. A method for reducing the number of prostate cancer cells in a subject, comprising

administering to the subject a therapeutically effective amount of the polynucleotide of claim 6, wherein the administration of the polynucleotide results in an immune response,

thereby reducing the number of prostate cancer cells in the subject.

44. A method for reducing the number of prostate cancer cells in a subject, comprising

administering to the subject a therapeutically effective amount of the antibody of claim 16,

thereby reducing the number of prostate cancer cells in the subject.

45. A kit for detecting an polynucleotide encoding NGEP in a sample, comprising

an isolated nucleic acid sequence of at least ten nucleotides in length that specifically binds to SEQ ID NO: 2 under highly stringent hybridization conditions; and

instructions for the use of the isolated nucleic acid sequence.

46. A kit for detecting an NGEP polypeptide in a sample, comprising

an monoclonal antibody that specifically binds to an antigenic epitope of SEQ ID NO: 1; and

instructions for the use of the antibody.